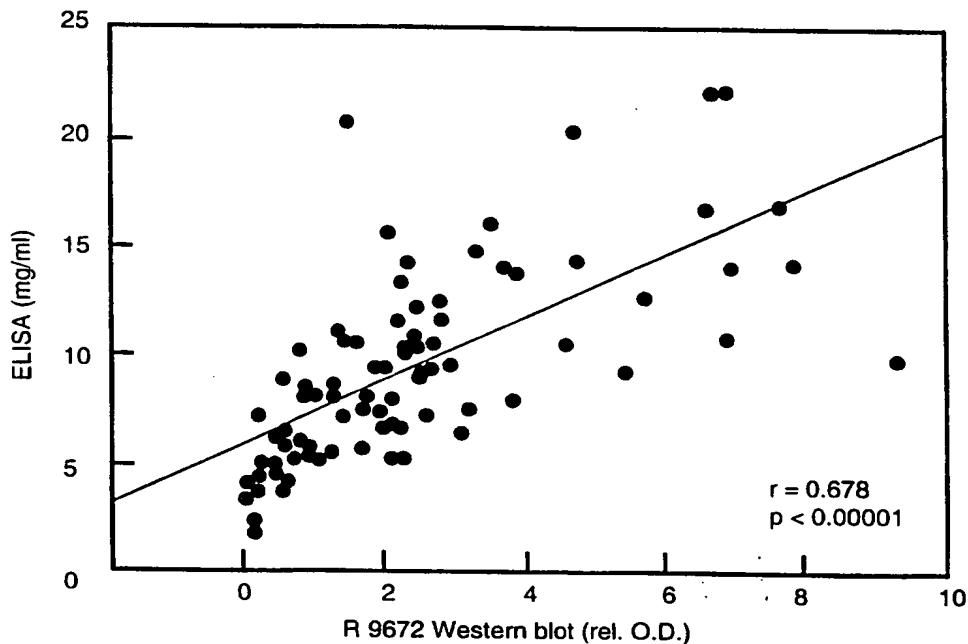




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : <b>G01N 33/68</b>		A3	(11) International Publication Number: <b>WO 00/25138</b>
			(43) International Publication Date: <b>4 May 2000 (04.05.00)</b>
(21) International Application Number: <b>PCT/EP99/08023</b>		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: <b>22 October 1999 (22.10.99)</b>			
(30) Priority Data: 60/105,458 23 October 1998 (23.10.98) US 60/107,434 6 November 1998 (06.11.98) US 99101377.2 26 January 1999 (26.01.99) EP			
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(74) Agents: MEYERS, Hans-Wilhelm et al.; P.O. Box 10 22 41, D-50462 Cologne (DE).			

(54) Title: METHODS OF DIAGNOSING OR PROGNOSING ALZHEIMER'S DISEASE



## (57) Abstract

A method for diagnosing or prognosing Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing Alzheimer's disease, comprising: determining a level, or an activity, or both said level and said activity, of transcription product and/or a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene in a sample from said subject; and comparing said level, or said activity, or both said level and said activity, of said transcription product and/or said translation product to a reference value representing a known disease or health status, thereby diagnosing or prognosing Alzheimer's disease in said subject, or determining whether said subject is at increased risk of developing Alzheimer's disease.

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## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>992365woMekk</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/ EP 99/ 08023</b>	International filing date (day/month/year) <b>22/10/1999</b>	(Earliest) Priority Date (day/month/year) <b>23/10/1998</b>
Applicant <b>NITSCH, ROGER et al</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **5** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  **Certain claims were found unsearchable (See Box I).**

3.  **Unity of invention is lacking (see Box II).**

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

**1**

**None of the figures.**

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-25

## Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

**1. Claims: 1-25**

Method of diagnosing Alzheimer's disease using cystatin C as a marker.

**2. Claims: 26-33**

Agents modulating activity of cystatin C.

**3. Claim : 34**

Method of identifying agents that modulate cystatin C.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/08023

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FUJIHARA S ET AL: "CEREBRAL AMYLOID ANGIOPATHY WITH THE DEPOSITION OF CYSTATIN C GAMMA-TRACE AND BETA-PROTEIN." KAMEYAMA, M. (ED.). INTERNATIONAL CONGRESS SERIES, NO. 999. BETA-AMYLOID PRECURSOR PROTEINS AND NEUROTRANSMITTER FUNCTION; EIGHTH WORKSHOP ON NEUROTRANSMITTERS AND DISEASES, TOKYO, JAPAN, JUNE 1, 1991. VII+107P. ELSEVIER SCIENCE PUBLISHERS B.V.: AMSTE, XP002110418 cited in the application the whole document	18,19, 21-25
Y	---	18,20
A	---	1-17

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

Date of mailing of the international search report

26 January 2000

20.06.2000

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 27 11 201 A (KLUTHE REINHOLD; SUEDHOFF ALBERT; SCHAEFFER GUNNAR) 21 September 1978 (1978-09-21) page 2 ---	18,20
X	VINTERS, H.V. ET AL.: "Immunoreactive A4 and Gamma-trace Peptide Colocalization in Amyloidotic Arteriolar Lesions in Brains of Patients with Alzheimer's Disease" THE AMERICAN JOURNAL OF PATHOLOGY, vol. 137, no. 2, August 1990 (1990-08), pages 233-240, XP000866515 page 237, column 2, paragraph 2 -page 238; table 1 ---	1-19, 21-25
X	MARUYAMA, KEIKO ET AL.: "Immunohistochemical Characterization of Cerebrovascular Amyloid in 46 Autopsied Cases Using Antibodies to beta-Protein and Cystatin C" STROKE, vol. 21, no. 3, March 1990 (1990-03), pages 397-403, XP000869870 table 2 ---	1-19, 21-25
A	PETURSDOTTIR I ET AL: "ESTIMATION OF CYSTATIN C IN DIFFERENT HUMAN EXTRACELLULAR FLUIDS." FIRST SYMPOSIUM ON HEREDITARY CENTRAL NERVOUS SYSTEM AMYLOID ANGIOPATHY, REYKJAVIK, ICELAND, SEPT. 2-3, 1985. ACTA NEUROL SCAND. (1986) 73 (3), 318., XP002110416 cited in the application abstract ---	1-17
X	LÖFBERG, H. ET AL.: "The Cerebrospinal Fluid and Plasma Concentrations of Gamma-Trace and Beta-2-Microglobulin at Various Ages and in Neurological Disorders" JOURNAL OF NEUROLOGY, vol. 223, no. 3, 1980, pages 159-170, XP002110417 cited in the application the whole document -----	18,19, 21-25
A		1-17

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2711201	A 21-09-1978	NONE	